Asymmetric Cycloaddition

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Catalytic Asymmetric Formation of δ-Lactones by [4+2] Cycloaddition of Zwitterionic Dienolates Generated from α,β-Unsaturated Acid Chlorides**

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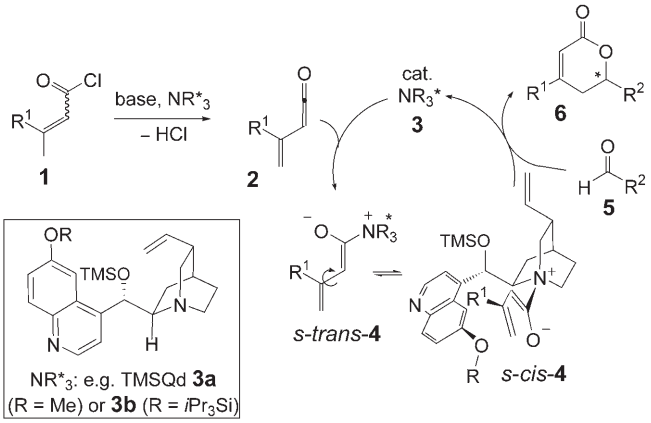
δ-Lactones are subunits of numerous natural and unnatural products that display a wide range of biological activity. In many cases they show high efficacy as antibacterial,[1] antiviral (HIV protease inhibitors),[2] anticancer,[3] immunosuppressive,[4] or cholesterol-lowering agents (HMGR inhibitors).[5] For example, the majority of statin drugs such as Lipitor and Zocor, the world's best-selling drugs in 2004, contain a β-hydroxy-δ-lactone moiety or the corresponding open-chain δ-hydroxy carboxylate form.[6] In addition, δ-lactones are very useful building blocks for the synthesis of bioactive compounds.[7]

Many approaches, most often multistep procedures, have been elaborated for the preparation of δ-lactones.[8] The most direct route to α,β-unsaturated δ-lactones is based on hetero-Diels–Alder (HDA) reactions.[9] In order to generate directly the desired oxidation state, a vinylketene equivalent such as a vinylketene acetal is required as the diene component. It has been reasoned though that twofold substitution at the butadiene terminus has a deleterious effect upon the enantioselectivity of HDA reactions, thus explaining why these dienes have been less frequently used in asymmetric HDA reactions than Danishefsky-type dienes.[10] Up to now, only three highly enantioselective, catalytic HDA-based methodologies using a vinylketene acetal have been reported,[11–13] which are all restricted to the use of Brassard-type dienes (1,3-dialkoxy-1-(trimethylsiloxy)butadienes)[14] and aromatic aldehydes[15] and which all require long reaction times (48–72 h) to provide useful yields.

We present herein a new concept for the synthesis of α,β-unsaturated δ-lactones **6** which circumvents the preformation, isolation, and purification of moisture- and acid-sensitive vinylketene acetals. Our work was based on the hypothesis that substituted vinylketenes **2** should be formed in situ by dehydrohalogenation of α,β-unsaturated acid chlorides **1** (Scheme 1).[16] Vinylketenes are known to be inherently unstable species,[17] but they might be trapped and at the same time activated as a diene component of a Diels–Alder reaction by an enantiopure tertiary amine, thus forming an enantiomerically pure zwitterionic dienolate **4**. This type of species was supposed to be reactive enough, in an *s*-cis conformation, to undergo [4+2] cycloadditions with aldehydes, by either a stepwise or a concerted mechanism. Our investigations were inspired by the tertiary-amine-catalyzed asymmetric synthesis of β-lactones from ketene via zwitterionic enolate intermediates.[18] Because of the considerable homology of **4** to vinylketene acetals, the intermediate formation of these dienolates was anticipated to overcome the pronounced tendency of vinylketenes to preferentially undergo [2+2] cycloaddition reactions.[19]



Scheme 1. Proposed [4+2] cycloaddition of α,β-unsaturated acid chlorides **1** with aldehydes **5** providing lactones **6**.

3,4-Dimethylpent-2-enoyl chloride (**1a**; $R^1 = i$Pr) and trichloroacetaldehyde (chloral, **5a**; $R^2 = CCl_3$) were chosen as model substrates for the development of this process. Initial experiments in acetonitrile at −15 °C using stoichiometric amounts of quinuclidine or triethylamine, both acting as a base as well as an achiral nucleophilic catalyst, provided the racemic δ-lactone **6a** ($R^1 = i$Pr, $R^2 = CCl_3$) in moderate yield (45% and 44%, respectively). Having demonstrated that the intended transformation is in principle possible, we sought an asymmetric version. After an initial screening of various combinations of cinchona alkaloid derivatives, stoichiometric non-nucleophilic tertiary amine auxiliary bases, and solvents, trimethylsilylquinidine (TMSQd, **3a**, 1.0 equiv), iPr$_2$NEt (Hünig's base, 2.0 equiv), and toluene were selected for further studies. At −15 °C the product was formed in 82% *ee*, albeit in very low yield (18%). One of the reasons for the poor performance was the incomplete conversion of **1a**

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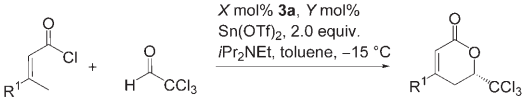
Supporting information for this article (including experimental details) is available on the WWW under http://www.angewandte.org or from the author.

(NMR monitoring). To facilitate the deprotonation process and to activate the aldehyde substrate, various metal triflate salts $M(OTf)_n$ were investigated as Lewis acid co-catalysts. The deprotonation process[20] was significantly improved with all investigated Lewis acids,[21] and the yield of **6a** increased to >70% in the presence of 20 mol% of $Er(OTf)_3$ (76%), $Sn(OTf)_2$ (75%), $Sc(OTf)_3$ (74%), or $Nd(OTf)_3$ (72%) when the acid chloride was added slowly over 30 min with a syringe pump. The enantiomeric excess was determined to be 82% in all experiments regardless of which Lewis acid co-catalyst was used. As the enantioselectivity does not depend upon the presence or absence of the metal triflate salt, we assume that the Lewis acid is not involved in the cycloaddition step itself and simply facilitates the dehydrochlorination of **1**. Increasing the temperature to 0°C gave similar results (70% yield with $Er(OTf)_3$, 80% *ee*), while decreasing the temperature to −40°C resulted in a dramatic decrease in yield (22% with $Er(OTf)_3$, 84% *ee*).

The investigation of the co-catalyst loadings revealed that reducing the amount of the Lewis acid to 10 mol% had almost no negative effect in the case of $Sn(OTf)_2$ (yield 72%, 82% *ee*), and even with as little as 1.4 mol% the reaction was still relatively efficient (60% yield, 82% *ee*). Decreasing the amount of TMSOd **3a** required a slower addition of the acid chloride to avoid massive polymerization. When **1a** was added over 120 min to a mixture of 20 mol% of **3a** and 10 mol% of $Sn(OTf)_2$, **6a** was obtained in 78% yield (82% *ee*, Table 1, entry 1).

Table 1: Preparation of α,β-unsaturated δ-lactones **6**.



1a–j **5a** **6a–j**

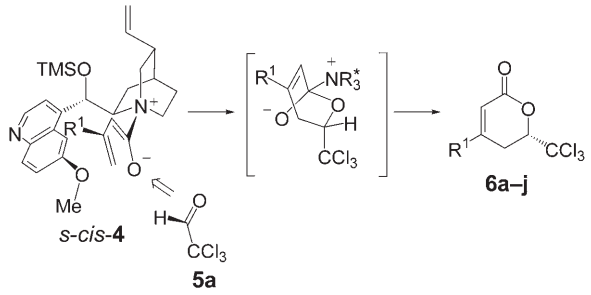
Entry	**1**	R^1	*X*	*Y*	Yield [%][a]	*ee* [%][b]
1	**1a**	*i*Pr	20	10	78	82
2	**1b**	Et	20	10	60	54
3[c]	**1c**	*i*Bu	40	20	73	70
4	**1d**	*c*Hex	20	10	75	83
5	**1e**	*t*Bu	20	10	58	95
6	**1e**	*t*Bu	40	20	80	95
7	**1f**	Ph	20	10	73	81
8	**1g**	Et_3Si	100	30	54	96
9[d]	**1g**	Et_3Si	40	20	43	96
10	**1h**	$BnMe_2Si$	100	30	47	92
11	**1i**	nPr_3Si	100	30	51	97
12	**1j**	nBu_3Si	100	30	61	97

[a] Yields of isolated products. [b] Determined by HPLC on a chiral column (Daicel OD-H). [c] Catalyst **3b** was used (see Scheme 1). [d] Acid chloride **1g** was added over 220 min.

Similar reaction conditions were applied to several alternative substrates **1b–f** bearing different branched or unbranched aliphatic, alicyclic, or aromatic groups R^1 (Table 1). δ-Lactones **6a–f** were formed in good yield and with up to 95% *ee* (Table 1, entries 1–7).[22] Both the enantioselectivity and the conversion of the acid chloride depended primarily upon the steric bulk of R^1. While with the unbranched Et substituent the *ee* was only moderate (Table 1, entry 2), the values were significantly higher and preparatively useful with branched or aromatic substituents (entries 3–7). Notably, even in the case of **1b** (R^1 = Et) C–C bond formation occurred with complete regioselectivity. With the bulky *i*Bu and *t*Bu substituents, higher catalyst and co-catalyst loadings were required to obtain high conversions (Table 1, entries 3 and 6).

To extend the synthetic value of the methodology, we turned our attention to substrates **1g–j** bearing a trialkylsilyl moiety, since the silyl groups would eventually permit further useful modifications of the δ-lactones after the cycloaddition step. The substrates were easily prepared by Ru-catalyzed hydrosilylation of tetrolic acid according to an efficient procedure developed by Trost et al.[23] While the silyl-containing substrates **1g–j** provided only moderate yields for the cycloaddition event due to a less efficient conversion of these acid chlorides, the obtained enantioselectivities were excellent (Table 1, entries 8–12).

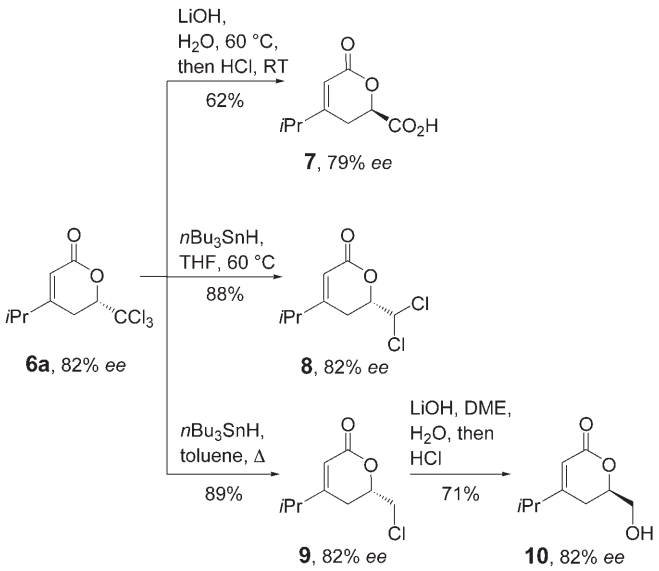
As a general trend, the remote control of the enantioselectivity depends largely on the steric bulk of R^1.[24] Based on MMFF calculations performed to determine the preferred conformation of the *cisoid* zwitterionic dienolate, we have developed a working hypothesis to rationalize the enantioselectivity for the formation of δ-lactones **6a–j** (Scheme 2).



Scheme 2. Rationalization of the remote stereocontrol.

Since the *re* face (relative to the C1 enolate atom) is shielded by the quinoline and the OTMS moieties, the aldehyde will attack from the better accessible *si* face. In the preferred orientation of the aldehyde in the transition state the residue R^1 and the CCl_3 group should point away from each other to avoid unfavorable steric interactions, thus explaining the large influence of R^1. Since no acyclic vinylogous Mukaiyama aldol products could be detected, this might indicate that the cycloaddition event proceeds by a concerted mechanism.

The trichloromethyl moiety in lactones **6** is a synthetically versatile functional group that can be readily converted into several valuable functionalities. Basic hydrolysis with LiOH in water at 60°C gave carboxylic acid **7** in 62% yield and without significant racemization (Scheme 3).[25] Selective partial reductive removal of the chlorine atoms of the trichloromethyl group was achieved using tributyltin hydride.[26] Performing the reduction in THF at 60°C afforded the dichloro derivative **8**,[27] whereas in refluxing toluene, the

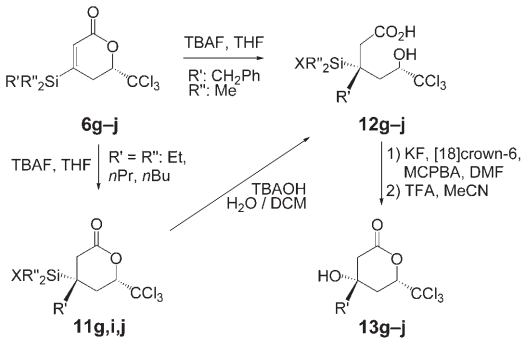


Scheme 3. Synthetic modification of the trichloromethyl group.

monochloro derivative **9** was obtained. The latter was smoothly hydrolyzed to give the primary alcohol **10**.

The silyl-substituted α,β-unsaturated δ-lactones **6g–j** were utilized to prepare saturated δ-lactones **13** carrying a tertiary hydroxy group at the β position (Table 2). Treatment

Table 2: Preparation of β-hydroxy δ-lactones **13** by alkyl migration/oxidation.[a]



Entry	Substrate	R′	R″	Yield **12** [%][b]	Yield **13** [%][b]	d.r. **13**[c]
1	**6g**	Et	Et	44	70	>99:1
2	**6h**	Bn	Me	92	85	25:1
3	**6i**	*n*Pr	*n*Pr	38	65	>99:1
4	**6j**	*n*Bu	*n*Bu	41	61	>99:1

[a] DCM = dichloromethane, MCPBA = *meta*-chloroperbenzoic acid, TFA = trifluoroacetic acid. [b] Yield of isolated product. [b] Determined from the ^{1}H NMR spectrum of isolated **13**.

of **6g–j** with 2.0 equiv of tetrabutylammonium fluoride (TBAF) in THF lead to diastereoselective migration of the benzyl or alkyl substituents by an intramolecular 1,4-addition. This reaction outcome is consistent with recent reports about the migration of allyl, benzyl, and phenyl groups within acyclic β-silyl enones or enoates upon treatment with TBAF.[28] To the best of our knowledge, the migration of simple alkyl substituents has not been reported before. The silanes **12** were subsequently oxidized under Tamao conditions to provide the tertiary alcohols **13**.[29,30] To accomplish this oxidation, the lactone moiety in **11**[31] had to be hydrolyzed first, presumably since the free carboxylate moiety intramolecularly activates the silyl group. In the case of the benzyl migration, the product is already ring-opened without a basic hydrolysis step.

In conclusion, we have developed a tertiary-amine-catalyzed enantioselective [4+2] cycloaddition of α,β-unsaturated acid chlorides and the electron-poor aldehyde chloral to provide synthetically versatile δ-lactone building blocks. The substituent at the β position can be varied to a large degree, and the trichloromethyl group made it possible to install several useful functional groups at the δ position. β-Hydroxy-δ-lactones possessing a quaternary stereocenter at the β position were diastereoselectively synthesized starting from the α,β-unsaturated δ-lactone carrying a trialkylsilyl substituent at the β position. Studies to further improve the scope of this novel approach are ongoing.

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[20] During the course of the reaction in toluene a precipitate of [*i*Pr$_2$NHEt]Cl is formed.

[21] Yield of **6a**: 55–76%; decreasing values in this order: M = Er^{III}, Sn^{II}, Sc^{III}, Nd^{III}, In^{III} = Cu^{II} = Yb^{III}, Li^{I}, Sm^{III}, Zr^{IV}, Al^{III} = Mg^{II}, Gd^{III} = Bi^{III}, Eu^{III}, Zn^{II}, Y^{III}. The combination of cinchona alkaloid derivatives and metal triflate salts was previously successfully applied to [2+2] cycloadditions of ketenes. See: S. France, M. H. Shah, A. Weatherwax, H. Wack, J. P. Roth, T. Lectka, *J. Am. Chem. Soc.* **2005**, *127*, 1206 and Ref. [18e].

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[30] The relative configuration of **13** was assigned by NOE experiments: see the Supporting Information for details.

[31] Product **11** is a mixture of three compounds with different groups X, which can be F, OH, or an O bridge in a dimeric species.

